Relationship between C-reactive protein and carotid artery intima media thickness in polycystic ovarian syndrome patients

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RELATIONSHIP BETWEEN C-REACTIVE PROTEIN AND CAROTID ARTERY INTIMA MEDIA THICKNESS IN POLYCYSTIC OVARIAN SYNDROME PATIENTS

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ABSTRACT

***Objective**: To determine relationship between CRP (C-reactive protein) concentration and CIMT (carotid artery intima media thickness) in young PCOS (polycystic ovary syndrome) females.*

***Design**: Cross-sectional*

***Setting**: Infertility outpatient clinic*

***Patients**: 70 PCOS patients (20-39 years old) and 70 healthy subjects as control.*

***Interventions**: CIMT was measured by Doppler ultrasound.*

***Main outcome measure**: Relationship between increased CRP level and CIMT.*

***Results**: Mean (±SD) serum CRP level was higher in PCOS patents (5.2 ± 2.8 mg/dL) in comparison to controls (4.9 ± 1.7 mg/dL), but the difference was not statistically significant (P= 0.482). However, mean (±SD) CIMT was significantly higher in PCOS group (0.65 ± 0.11 mm) compared to controls (0.59 ± 0.21 mm); P= 0.016. Although with increased CRP level, CIMT increased in PCOS patients, the relationship was not statistically significant (P= 0.065, r= 0.886). Also there was a relationship between age and CIMT but it was not statistically significant (P= 0.07, r= 0.215). However, relationships between CIMT and BMI (P= 0.04, r= 0.571) and between CIMT and waist circumference (P= 0.028, r= 0.36) were statistically significant. Based on regression analysis serum CRP level (P= 0.055, 95% CI= 1.589-73.713) and BMI (P= 0.051, 95% CI= 1.379-2.412) were independent variables which affected CIMT.*

***Conclusion**: CRP was elevated in PCOS patients compared to controls, but the difference was not statistically significant. Therefore, measuring CRP in PCOS patients should be interpreted with keeping in mind other CVD risk factors in these patients such as fasting blood sugar, lipid profile, and most importantly BMI.*

***Key words**: Polycystic ovary syndrome (PCOS), carotid intima media thickness (CIMT), C-reactive protein (CRP); atherosclerosis.*

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Introduction

Polycystic ovary syndrome (PCOS) is one the most common reproductive endocrine diseases affecting 5-7% of female population in reproductive age[1]. PCOS is characterized by chronic anovulation, excess androgen, and insulin resistance. PCOS most often is accompanied by hypertension, obesity, diabetes mellitus (DM) type II, and insulin resistance[2]. Females with PCOS may be the largest female population with premature atherosclerosis and cardiovascular diseases (CVD) events[3, 4]. However, according to a meta-analysis performed in 2012[1], there is still controversy whether the observed CVD risk factors in PCOS patients really increase CVD events and subclinical atherosclerosis in this population[1].

In early stages of atherosclerosis, carotid artery intima media thickness (CIMT) increases. In assessment of subclinical atherosclerosis, the most important with least complications is to measure CIMT. Prospective studies have demonstrated that increased CIMT is a strong predictor for coronary artery events and cerebrovascular diseases related

to CVD risk factors including older age, dyslipidemia, and obesity[1]. This state of increased CIMT has also been implicated in PCOS patients in several studies[5-7], though there is evidence that CIMT was not higher in PCOS patients (whether in hyperandrogenic or non-hyperandrogenic patients) compared to matched Korean controls[5].

Inflammation is a risk factor in progression of atherosclerosis[8]. In former studies it has been shown that C-reactive protein (CRP), as a marker for inflammation, predicts stroke, myocardial infarction (MI), peripheral vascular diseases, and sudden death[9]. Although it seems that inflammation markers have more significant relationship with onset of atherosclerosis compared to lipid profile, the relationship between increased CRP level and increased CIMT is still controversial, though recent evidence suggests that there is a relationship[10, 11]. In a study on PCOS patients, it was reported that fasting CRP level was significantly higher than control group[12].

In this study, we intended to measure CIMT, as an indicator of subclinical atherosclerosis, in PCOS patients and determine its relationship with serum CRP concentration. If a significant relationship is found between high CRP level and increased CIMT, atherosclerosis can be slowed down via screening and monitoring this high risk group by serum CRP level as well as appropriate preventive measures including but not limited to lifestyle modifications and even medical therapeutic interventions.

Materials and methods

Study population

In this cross-sectional study, 70 patients (20-39 years old) with the diagnosis of PCOS according to the Rotterdam criteria (to criteria were required of 3 criteria to make the diagnosis of PCOS) were included[13]. These patients presented to our tertiary infertility center. The sampling was done via convenience method. The sample size was determined according to the Cohen table (alpha= 5%, B= 20%, power= 80%). Inclusion criteria consisted of age range between 20 and 39 years old, no pre-existing medical condition, not taking hormonal medications, body mass index (BMI) between 18-30 kg/m2 (neither underweight, nor obese persons), and not having metabolic syndrome[14] according to the definition by the 2001 National Cholesterol Education Program/ATP III (defined as waist circumference > 88 cm, serum triglyceride > 150 mg/dL, blood pressure > 130/85 mmHg, fasting plasma glucose > 100 mg/dL, and serum HDL < 40 mg/dL). Control group consisted of patients who presented to the infertility clinic, but the cause of infertility was not PCOS. They were matched with the PCOS group regarding age and BMI. Exclusion criteria for both PCOS and control groups were history of premature coronary artery disease in the family, stroke, any vascular disease, any chronic inflammatory condition (e.g., rheumatoid arthritis, systemic lupus erythematosus, connective tissue diseases, chronic infection), and cigarette smoking.

Data gathered

A checklist containing the required data was filled out for the patients. The data were age, weight, height, waist circumference, buttock circumference, systolic and diastolic blood pressure, history of previous diseases, and medication history. Then, serum levels of total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, FSH (follicle stimulating hormone), LH (luteinizing hormone), prolactin, testosterone, fasting blood glucose (FBS), and CRP were measured by the hospital's laboratory. CRP was measured by Cobas Integra® via biochemical analysis. All CRP measurements were done in a single laboratory. Normal range was less than 5 mg/dL.

CIMT measurement

To measure CIMT, the patients underwent Doppler ultrasound using B-mode method by a board-certified radiologist at our hospital. Doppler ultrasound of both common carotid arteries was done and at the best point, the distance between intima and media was measured. Mean of the two measurements on both sides made for each patient was regarded as CIMT for that particular patient.

Statistical analyses

These were accomplished by the SPSS software for Windows (ver. 16.0). To express data, descriptive indices such as frequency, percentage, mean, and standard deviation (SD) were used. To compare the categorical variables between PCOS and control groups, the Chi-squared test was done and for continuous variables the student t-test was done.

Ethics

The study proposal was first prepared and submitted to the Ethics Committee of Tehran University of Medical Sciences and after getting approval from this committee the study was initiated. The study protocol was in conformity with the ethical guidelines of the 1975 Declaration of Helsinki[15].

Results

Mean (±SD) ages of PCOS and control groups were 28.9 (±2.8) and 27.9 (±2.7) years, respectively (P = 0.104). Table 1 presents BMI, waist circumference, hip circumference, and systolic and diastolic blood pressure measurements in the two groups. As expected, both systolic blood pressure and diastolic blood pressure were significantly higher in PCOS patients.

	PCOS group	Control	P value
BMI, kg/m^2	25.4 (±1.8)	25.3 (±1.7)	0.258
Waist circumference, cm	98.4 (±1.8)	93.7 (±5.6)	0.62
Hip circumference, cm	109.8 (±13.5)	102.9 (±18.3)	0.37
Waist-to-hip ratio	0.9 (±0.17)	0.82 (±0.13)	0.12
Systolic blood pressure, mmHg	121.8 (±9.6)	117.9 (±7.2)	0.025
Diastolic blood pressure, mmHg	81.1 (±10.8)	76.1 (±6.5)	0.005

Table 1: Comparison of mean (±SD) BMI, waist and buttock circumferences, and blood pressure between polycystic ovary syndrome (PCOS) patients and controls.

Regarding laboratory findings, FBG, triglyceride, and total cholesterol were higher significantly in PCOS group (Table 2). All three hormones measured here including FSH, LH, and testosterone levels were significantly higher in the patients compared to controls (Table 3).

	PCOS	Control	P value
Fasting blood glucose, mg/dL	99.8 (±21.3)	89.2 (±15.9)	0.001
Triglyceride, mg/dL	162.8 (±69.4)	139.5 (±51.7)	0.022
Total cholesterol, mg/dL	196.2 (±50.7)	170.9 (±58.7)	0.002
HDL, mg/dL	46.2 (±14.9)	52.7 (±13.6)	0.003
LDL, mg/dL	127.7 (±31.8)	119.4 (±37.7)	0.099

Table 2: Comparison of mean (SD) lipid profile and fasting blood glucose between PCOS and control groups.

Mean (±SD) serum CRP level was higher in PCOS patients (5.2 ± 2.8 mg/dL) in comparison to controls (4.9 ± 1.7 mg/dL), but the difference was not statistically significant (P= 0.482).

However, mean (±SD) CIMT was significantly higher in PCOS group (0.65 ± 0.11 mm) compared to controls (0.59 ± 0.21 mm); P= 0.016.

	PCOS	Control	P value
FSH, IU/L	8.2 (±3.2)	5.6 (±2.1)	0.039
LH, IU/L	15.8 (±5.4)	3.2 (±2.5)	0.001
Testosterone, IU/L	2.8 (±1.1)	1.5 (±0.7)	0.04

Table 3: Comparison of mean (SD) serum FSH, LH, and testosterone levels between PCOS patients and controls.

According to correlation analysis, no significant relationship was detected between serum CRP level and CIMT, however with increased CRP level, CIMT also showed an increased pattern (P= 0.065, r= 0.886). Also there was a relationship between age and CIMT but it was not statistically significant (P= 0.07, r= 0.215). However, relationships between CIMT and BMI (P= 0.04, r= 0.571) and between CIMT and waist circumference (P= 0.028, r= 0.36) were statistically significant.

	Normal CIMT	Increased CIMT	P value
Age, year	30 (±2.1)	28.3 (±2.4)	0.059
BMI, kg/m^2	25.3 (±1.7)	25.3 (±1.9)	0.832
Total cholesterol, mg/dL	172.2 (±37.5)	212.6 (±52.8)	0.08
Triglyceride, mg/dL	154.8 (±62.6)	161.6 (±66.3)	0.646
LDL-cholesterol, mg/dL	106.7 (±31.1)	128.2 (±39.5)	0.065
HDL-cholesterol, mg/dL	48.5 (±16.3)	42.9 (±12.1)	0.212
Systolic blood pressure, mmHg	121.4 (±6.8)	122.4 (±12.8)	0.808
Diastolic blood pressure, mmHg	80.8 (±6.9)	82.3 (±12.9)	0.251
CRP level, mg/dL	5.03 (±1.82)	5.47 (±1.62)	0.065
Fasting blood glucose, mg/dL	96.7 (±14.9)	104.1 (±26.5)	0.378

Table 4: Comparison of the studied variables between normal CIMT (< 0.6 mm) and increased CIMT (> 0.6 mm) in PCOS patients.

	B	SE	df	Significance	95% CI
Age	- 0.012	0.959	1	0.990	0.151-6.470
BMI	- 0.313	0.336	1	0.051	1.379-2.412
Total cholesterol	0.003	0.060	1	0.955	0.892-1.129
Triglyceride	0.003	0.008	1	0.751	0.986-1.020
LDL-cholesterol	0.017	0.018	1	0.352	0.982-1.053
HDL-cholesterol	0.024	0.046	1	0.597	0.937-1.121
Systolic blood pressure	- 0.012	0.055	1	0.829	0.887-1.101
Diastolic blood pressure	0.073	0.103	1	0.476	0.880-1.317
CRP level	2.382	0.979	1	0.055	1.589-73.713
Fasting blood glucose	0.052	0.093		0.576	0.878-1.263

Table 5: Regression analysis of the studied variables and carotid artery intima media thickness in PCOS patients.

Based on CIMT, the PCOS patients were divided into two groups of normal CIMT (< 0.6 mm) and increased CIMT (> 0.6 mm). Table 4 depicts comparison of the studied variables between normal and increased CIMT in PCOS patients. As shown, no significant difference in terms of studied variables was observed between normal and increased CIMT groups in PCOS patients.

Regression analysis showed that serum CRP level and BMI were independent variables which affected CIMT (Table 5).

Conclusion

The results of the present study indicated that plants can remove contaminants. In the present study, matricaria chamomilla could remove TPH at a maximum rate of 49.73 and 51.97% % in concentration of .25 for light and heavy types of petroleum, respectively. Concentration of 4% was the critical concentration for matricaria chamomilla in both types of petroleum because in this concentration the plant cannot grow and the microbial population was lower compared to other contamination concentrations. Nonionic surfactant Tween 80 had a better performance in regard with removal percentage of TPH and an increase in microbial population compared to anionic surfactant and the treatment without surfactant in both types of petroleum.

Discussion

Recent studies suggest that CDV risk factors are increased in PCOS patients[1]. Evidence suggests that coronary artery disease and stroke are two times more likely to occur in PCOS patients a recent meta-analysis showed women with PCOS[16, 17]. CIMT has been used in several studies in PCOS patients in order to demonstrate subclinical atherosclerosis. There is inconsistency between the studies about the exact role of CIMT and comparable to the current results, they showed significantly increased CIMT in PCOS patients which is indicative of subclinical atherosclerosis[4, 6]. Although there is inconsistency in related studies, but a meta-analysis of 19 articles performed by Meyer et al.[1] showed that mean difference in CIMT among women with PCOS compared with controls was 0.072 mm (95% CI, 0.040-0.105; P < 0.0001) for highest quality studies, and 0.084 mm (95% CI, 0.042-0.126; P < 0.0001) for good quality studies[5]. However, some studies did not find any difference between PCOS and controls. For example, Kim et al.[5] did not find any difference in terms of CIMT between Korean PCOS and age-matched controls. In their study on 56 PCOS cases and 56 controls,

Mean (SD) CIMT in cases and control groups were 0.49 (± 0.09) mm and 0.50 (± 0.11), respectively; P= 0.562. Several factors can explain inconsistency between studies. Considering the complex nature of PCOS, age, BMI, low sample size, the method of CIMT measurement, and so forth are the possible causes of this controversy. Mean values for BMI and age of PCOS cases in Korean study were 21.2 kg/m2 and 30.9 years, whilst these figures in our study were 25.4 kg/m2 and 28.9 years. We decided to include PCOS patients with BMI ranging from 18-30, and as expected mean BMI value of the recruited cases was high, which we think is more representative of PCOS patients routinely visited in our clinic.

Serum CRP level is an established inflammatory marker, and as stated previously, is a potential predictor for CVD and stroke[9]. By measuring this marker in PCOS cases and comparing it with controls, we intended to find whether this marker can be used as an easy and accessible rapid way to assess CVD in such patients. The results obtained showed that this marker, although was higher in PCOS compared to control group, the difference was not statistically significant.

Increased CRP levels in PCOS patients has been reported earlier[18, 19]. Cascella et al.[12] who noted significant increase in mean CRP level in PCOS patients (1.9 mg/L) vs. controls (0.8 mg/L). They also reported that CRP positively affected CIMT. They also found increased levels of other inflammatory markers including fibrinogen, white blood cell count, and plasminogen-activated inhibitor-1 levels in PCOS compared to controls. In the latter mentioned study, mean BMI value of PCOS patients was 28.5 which is higher than BMI of our patients. However, this is in consistent with Kim et al. study[5] who reported median (range) of highly sensitive C-reactive protein (hs-CRP) in PCOS and control group as 0.01 (0.01-1.15) and 0.02 (0.01-0.29) mg/dL, respectively; P= 0.28.

The role of weight and its relationship with CRP level should be considered here. Considering several factors contribute to CRP level such as obesity, hypertension, dyslipidemia, it may be stated that the factor or factors which determine CRP level in PCOS patients are different in this popula-

tion, and therefore this variation of contributing factors adjust various results regarding CRP. Mohlig et al.[20] noted that serum CRP level in PCOS patients is related to weight (i.e., obesity) rather than PCOS per se. In their study on 57 PCOS patients with a control group, they reported that neither CRP nor IL-6 were significantly elevated in lean or obese PCOS patients compared with age-matched lean or obese controls. But BMI itself, not PCOS, was the main factor related to elevated CRP and chronic inflammation. The two groups studied here had no difference regarding BMI. This is in agreement with Mohlig et al. study[20] considering the role of BMI and weight excess in chronic inflammation. These findings are in agreement with another study by Oh et al.[21]. Their study included 30 lean (BMI< 23 kg/m2) PCOS patients and a control group. They noted that even though serum hs-CRP levels were higher in lean women with PCOS (mean (SD)= 0.72±0.20) than in control group (mean(SD)= 0.27±0.04 mg/L), the difference was no longer significant after adjusting for BMI. According to their multiple regression analysis, BMI, systolic blood pressure, and insulin-mediated glucose uptake were predicting factors for CRP. In other words, established CVD risk factors which are present more frequently in PCOS patients than control subjects are the determining factors in CRP level. We also observed a significant difference with respect to fasting blood glucose, HDL, triglyceride, and total cholesterol between PCOS and control groups, but not LDL concentration. About CIMT, neither CRP nor other CVD risk factors were different between normal and elevated CIMT.

In conclusion, CRP was elevated in PCOS patients compared to controls, but the difference was not statistically significant. Therefore, measuring CRP in PCOS patients should be interpreted with keeping in mind other CVD risk factors in these patients such as fasting blood sugar, lipid profile, and most importantly BMI.

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